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A Comparative Analysis of Toxicity Models

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PREFACE

This paper reports the work performed by the Institute for Defense Analyses for the U.S. Army Office of Surgeon General and the Joint Staff, Director for Joint Requirements Office-CBRD Defense (J8 JRO-CBRD) in partial fulfillment of the task entitled "Revision of NATO AMedP-8 'Planning Guide for the Estimation of Battle Casualties.'"

The authors wish to thank Douglas Sommerville of Edgewood Chemical Biological Center, Nafis Upshur, and Margaret Porteus, who reviewed this paper.

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SUMMARY

In this paper casualty estimates and predicted injury severity levels obtained using different toxicity models are compared for inhalation exposure to assess the significance of using different toxicity models for military medical planning. This information is intended to aid in the determination of an appropriate toxicity model to be incorporated into existing and future casualty estimation methodologies.

The toxicological effect of exposure to chemical warfare agents is a complex phenomenon resulting from environmental conditions external to the body and processes occurring within the body. The primary external determinants of the toxicological effect are the agent concentration, the duration of exposure, and, presumably, the manner in which the agent concentration fluctuates through time. Meanwhile, dynamic internal processes such as agent uptake, distribution, elimination, and metabolism also contribute to determining the magnitude of the toxicological effect.

Haber's Law, the integrated toxic load model, and the mean concentration toxic load model have been previously investigated for use in hazard assessments.[1] These three toxicity models only consider the external determinants and do not address any of the internal processes. In an effort to expand upon the current methods of modeling toxicity, an unconventional approach to compartmental toxicokinetic modeling is examined. This examination will address both the external conditions, as well as generalized representations of the internal processes that interact to produce the toxicological effect. By incorporating representations of the dynamic internal processes in this model, a mechanistic basis for modeling the toxicity of time-varying agent concentrations is provided.

Haber's Law, the integrated toxic load model, the mean concentration toxic load model, and a two-compartment toxicokinetic model are applied to an illustrative scenario to assess the significance of using different toxicity models in casualty estimations for military medical planning. The output of each toxicity model is used to classify personnel by their casualty status (no effects/miosis, casualty, fatality) as well as by

[1] Sommerville, D.R.; Park, K.H.; Kierzewski, M.O.; Dunkel, M.D.; Hutton, M.I.; Pinto, N.A.;"Toxic Load Modeling," Inhalation Toxicology. 2nd Edition, Eds. Salem, H.; Katz,S. Boca Raton, FL: CRC Press, 2006. pp. 141-142. Hilderman, T.L.; Hrudey, S.E.; Wilson, D.J. "A Model for Effective Toxic Load from Fluctuating Gas Concentrations," *Journal of Hazardous Materials* 64 (1999) pp. 118-119.

injury severity. The resulting casualty estimates and the injury severity predictions for each toxicity model are then compared to each other.

Focusing on casualty status, the comparison demonstrates that, for the particular illustrative scenario used in this comparison, the use of Haber's Law generally predicts greater numbers of casualties relative to the other models. The mean concentration toxic load model predicts the fewest number of casualties. The integrated toxic load model and the two-compartment toxicokinetic model predict the same number of casualties. Because these results are based on only a single scenario, it is not suggested that these results will always hold true under different scenarios. A more thorough investigation encompassing a much wider range of scenarios is currently being performed by the authors of this paper so that the differences between the toxicity models with regard to casualty estimation can be better understood.

I. TOXICITY MODEL DESCRIPTIONS

A. HABER'S LAW

Current toxicity models, such as Haber's Law and the toxic load model, suffer from their inability to specifically address the processes occurring within the body. For a fixed ventilation rate, which is assumed throughout the present paper, Haber's Law dictates that the dosage is the sole determinant of the toxicological effect in a specified percentage of the population. When expressed mathematically, Haber's Law states that for exposure to any agent concentration, C, beginning at an initial time, t_i, and ending at a final time, t_f, that produce a given toxicological effect, e, in a given percentage of the population, p, the product of C and $(t_f - t_i)$ is a constant $K_{e,p}$. Haber's Law is shown in Equation 1.

$$C \times \left(t_f - t_i\right) = K_{e,p} \tag{1}$$

When this principle is applied to a time-varying agent concentration, the instantaneous concentration must be integrated with respect to time. Thus, for any time-varying agent concentration function, $C(t)$, beginning at t_i and ending at t_f that produces a given toxicological effect, e, in a given percentage of the population, p, the integral of the instantaneous concentration across the exposure duration is a constant, as shown in Equation 2.

$$\int_{t_i}^{t_f} C(t)dt = K_{e,p} \tag{2}$$

Haber's Law implies that the degree of injury resulting from an exposure is linear with respect to both agent concentration and exposure duration.[2] This suggests that protracted, low-concentration exposures will produce the same toxicological effect as short-duration, high-concentration exposures given the same dosage. Although this assumption may be true for some agents in the exposure durations of interest, it is certainly not true for all agents at all exposure durations. For example, typically there is a concentration at which no observable effects will be encountered for a particular agent irrespective of the duration of exposure.

[2] The exposure duration does not necessarily correspond to the time at which signs or symptoms become evident.

B. TOXIC LOAD

Laboratory animal experiments have shown that Haber's Law does not apply to several chemical warfare agents, such as GB, GD, GF, and HD.[3] Given the same dosage, the effect of exposure to any of these agents has been observed to be more severe when the exposure duration is short rather than long. This is likely due to the internal processes that eliminate and effectively detoxify the agent within the body over the course of protracted exposures. These experiments revealed that the trend in ECt_p (or LCt_p) values for various exposure durations was nonlinear with respect to agent concentration.[4] This relationship has been modeled by raising the agent concentration to an exponent, n_e, as shown in Equation 3.

$$C^{n_e} \times (t_f - t_i) = T_{e,p} \tag{3}$$

This relationship is known as the toxic load model. The toxic load value, $T_{e,p}$, is the determinant of the toxicological effect in a specified percentage of the population. The value of the toxic load exponent, n_e, is determined through animal experiments utilizing several different exposure durations. The toxic load exponent can be viewed as a representation of the cumulative effect of many different processes that interact to produce a toxicological effect.[5] If the value of the toxic load exponent is greater than one, then the model predicts that short-duration, high-concentration exposures will produce more severe toxicological effects than long-duration, low-concentration exposures given that the dosages are the same in the two exposures. For most nerve agents, the value of the toxic load exponent is greater than one.[6] The opposite is true if the value of the toxic load exponent is less than one: short-duration, high-concentration exposures will produce less severe toxicological effects than long-duration, low-concentration exposures given that the dosages are the same in the two exposures. It is important to understand that the animal experiments used to determine the value of the toxic load exponent were conducted with exposures to constant agent concentrations.[7]

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[3] U.S. Army, U.S. Marine Corps, U.S. Air Force, U.S. Navy *Potential Military Chemical/Biological Agents and Compounds FM 3-11.9* (January 2005) Appendix H.

[4] ECt_p is the dosage that would cause the specified effects in p percent of the exposed population. For the case of LCt_p, the specified effect is death.

[5] Rozman, K.; Doull, J. "Dose and Time as Variables of Toxicity," *Toxicology* 144 (2000) p. 173.

[6] FM 3-11.9. op cit. Appendix H.

[7] Mioduszewski, R.; Manthei, J.; Way, R.; Burnett, D.; Gaviola, B.; Muse, W.; Thompson, S.; Sommerville, D.; Crosier, R. "Interaction of Exposure Concentration and Duration in Determining Acute Toxic Effects of Sarin Vapor in Rats," *Toxicological Science* 66 (2002a) p. 179; Bide, R.W.; Risk, D.J.; "Inhalation Toxicity in Mice exposed to Sarin for 20-270 min," *Journal of Applied Toxicology* 24 (2004). p. 461; Matson, K.L.; Benton, B.J.;Crouse, C.L.; Sommerville, D.R.; Miller, D.; Scotto, J.; Evans, R.A.; Burnett, D.C.; McGuire, J.M.; Gaviola, B.I.; Jarvis, J.; Crosier, R.B; Jakubowski, E.M.; Whalley, C.E.;Anthony, J.S.; Hulet, S.W.; Dabisch, P.A.; Reutter, S.A.; Forster, J.S.;

Although the toxic load model provides a good fit to the data resulting from these constant concentration experiments, it remains uncertain whether this relationship holds when applied to time-varying agent concentrations.

1. Integrated Toxic Load Model

The questionable applicability of the toxic load model under time-varying concentration is further complicated by the fact that there are two different proposed methods by which the toxic load model may be applied to a time-varying agent concentration. The first is very similar to the way in which Haber's Law is applied to a time-varying concentration except that the instantaneous agent concentration is raised to the power of the toxic load exponent, as shown in Equation 4.[8]

$$\int_{t_i}^{t_f} C(t)^{n_e}\, dt = T_{e,p} \tag{4}$$

2. Mean Concentration Toxic Load Model

A different approach to applying the toxic load model to time-varying agent concentrations involves the mean concentration, C_μ, over the time interval of the exposure, as shown in Equation 5.

$$C_\mu = \frac{\int_{t_i}^{t_f} C(t)dt}{t_f - t_i} \tag{5}$$

The mean concentration may then be substituted into the expression for the toxic load model given previously in Equation 3. This substitution results in the expression given in Equation 6.[9]

Mioduszewski, R.J.; Thomson, S.A.; *Low Level Effects of VX Vapor Exposure on Pupil Size and Cholinesterase Levels in Rats, ECBC-TR-428*, U.S. Army Edgewood Chemical Biological Center Aberdeen, MD 2005, p. 11; Anthony, J.S.; Haley, M.; Manthei, J.; Way, R.; Burnett, D.; Gaviola, B.; Sommerville, D.; Crosier, R.; Mioduszewski, R.; Thomson, S.;Crouse, C.; Matson, K.; "Inhalation Toxicity of Cyclosarin Vapor in Rats as a Function of Exposure Concentration and Duration: Potency Comparison to Sarin," *Inhalation Toxicology* 16 (2004) p. 105.

[8] ten Berge, W.F.; Zwart, A.; Appleman, L.M.; "Concentration-Time Mortality Response Relationship of Irritant and Systematically Acting Vapors and Gases," *Journal of Hazardous Materials* 13 **(**1986) p. 308; Hilderman. op cit. pp. 118-119; Yee, E. "An Impact-Effect Mathematical Model Incorporating the Influence of Exposures to Fluctuating concentrations in a Dispersing Plume of Pollutant in the Atmosphere," *Journal of Exposure Analysis and Environmental Epidemiology* 9 (1999) pp. 300-301.

[9] Hilderman. op cit. p. 118.

$$C_{\mu}^{n_e} \times \left(t_f - t_i\right) = \left(\frac{\int_{t_i}^{t_f} C(t)dt}{t_f - t_i} \right)^{n_e} \times \left(t_f - t_i\right) = T_{e,p} \qquad (6)$$

This approach will be referred to as the mean concentration toxic load model. This model assumes that a time-varying agent concentration can be reasonably approximated by a constant average concentration. This assumption is valid for constant concentration exposures because the mean concentration is equal to the instantaneous concentration throughout the exposure, but this assumption remains untested for exposures involving time-varying agent concentrations. A key problem with this model is that the manner in which the exposure duration is defined can have a significant effect on the predicted toxicological effect. For example, the exposure duration can be defined as the period in which the concentration is non-zero, which can lead to a very small mean for exposures involving long periods of low concentration. Alternatively, the duration may be defined as the period during which the concentration is above some threshold, in which case a threshold must be chosen. This threshold itself may be dependent on the exposure duration. Furthermore, there does not seem to be a straightforward method for defining the exposure duration when exposures are intermittent. In such cases, including periods of *zero agent concentration* that are interspersed between periods of *non-zero concentration* in the definition of exposure duration can significantly reduce the predicted injury severity. This effect is especially significant for attacks involving multiple munitions or variable wind direction. In the present paper, the exposure duration is defined as the time from the first non-zero concentration until the last non-zero concentration at a particular personnel location. Thus, this definition includes any periods of zero concentration that may occur between the first and last non-zero concentrations at a location.

Both the integrated toxic load model and the mean concentration toxic load model produce the same results under the condition of constant agent concentration, but can behave differently when concentrations do not remain constant throughout the exposure. Until experimental data are available for time-dependent concentration exposures, it is not possible to distinguish which version of the toxic load model is most appropriate.

C. TWO-COMPARTMENT TOXICOKINETIC MODEL

Compartmental toxicokinetic models approach toxicity quite differently. These models ascribe the magnitude of the toxicological effect to the quantity of an agent at its target within the body. In order to make this correlation, internal processes such as agent uptake, distribution, and elimination are considered. These processes are modeled by treating the body as a collection of distinct compartments through which there is a flux of agent. Typically, these models require extensive experimental data to determine the rates of the internal processes. Although the processes of uptake, distribution, and elimination are real physiological processes and are commonly interpreted as such in toxicokinetic models, they are not intended to be viewed in this way for the model used in the present paper. By avoiding a correlation to real phenomenon, only the structure and mechanistic nature of kinetic modeling is captured in the model. This allows for flexibility in the model, because it does not have to conform to realistic rate values for individual processes. It also avoids the need for extensive experimental data. Despite lacking realistic rates for individual processes, the combination of these rates produces a realistic depiction of the relationship between dosage and exposure duration. Similarly, the compartments are not intended to necessarily represent specific organs or tissues. The non-anatomical nature of the model allows a single model to be generic enough to address many different agents with differing mechanisms of toxicity. Given these considerations, a clarification of the nomenclature that will be used to describe this model is necessary. The names assigned to the various processes in the model, i.e. uptake, distribution, and elimination, are descriptors of the movement of agent within the model structure, not the movement of agent within the body.

1. Model Structure

The compartmentalized representation of the body allows the quantity of agent in the different non-anatomical regions to be mathematically described by a system of differential equations. The compartmental model examined in the current analysis consists of only two compartments and can be described by a system of two differential equations, Equation 7 and Equation 8. The graphical representation of the model, given in Figure 1, provides greater insight into the mechanistic nature of the model.

$$\frac{dQ_1}{dt} = bC(t) - k_3Q_1 - k_1Q_1 + k_2Q_2 \tag{7}$$

$$\frac{dQ_2}{dt} = k_1Q_1 - k_2Q_2 \tag{8}$$

Q_1 is the quantity of agent in compartment #1 and Q_2 is the quantity of agent in compartment #2. The constant, *b*, defines the rate of agent uptake into compartment #1. The first-order rate constants k_1 and k_2 govern the exchange of agent between compartment #1 and compartment #2. The first-order elimination rate constant, k_3, defines the rate at which the agent is removed from the system.

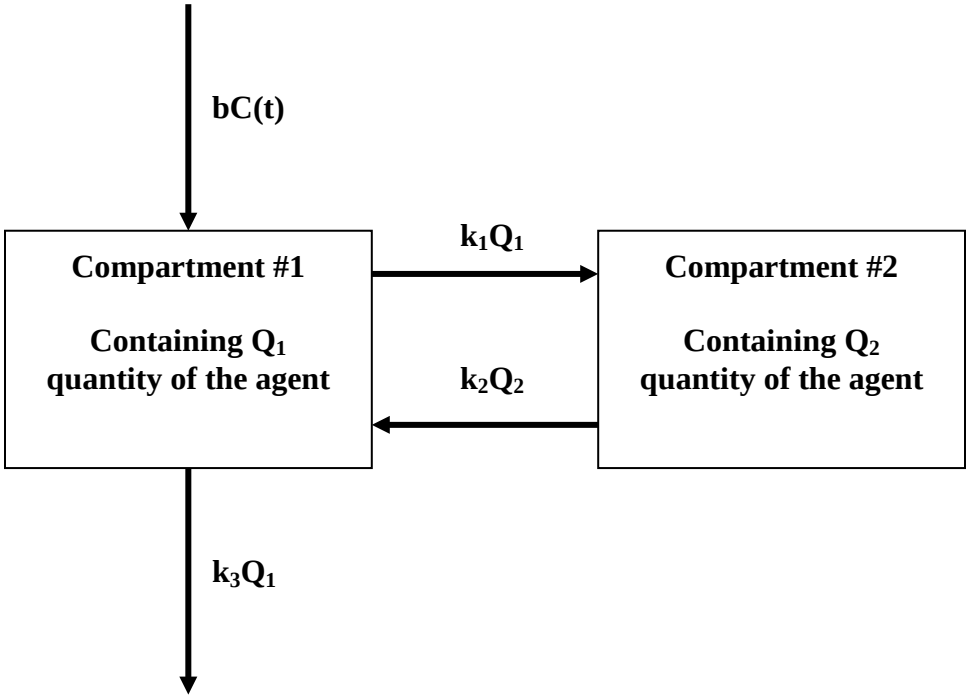

Figure 1. A Graphical Depiction of the Two-Compartment Toxicokinetic Model

The agent enters the system from the environment through compartment #1 exclusively. From compartment #1, the agent can then be distributed to compartment #2 or be eliminated from the system, either by being detoxified or returning to the environment. Compartment #2 cannot directly interact with the environment.

2. Rate Constant Determination Methodology

The primary limitation to the implementation of physiologically-based, compartmental toxicokinetic models in casualty estimation is the expense and time required to determine the rates of the various internal processes. Generally, the rates of these internal processes and the general behavior of a particular agent within the body are determined through an extensive series of animal experiments in which the concentrations of the agent in various tissues, organs, and fluids are monitored during or after exposure. An alternative approach for determining rate constants was examined that

avoids this difficulty while retaining the mechanistic basis for the application to time-varying agent concentrations. This alternative method for calculating rate constants was used to develop the toxicokinetic model for this comparison, but could potentially be used to develop kinetic models for the casualty estimation of exposure to any agent demonstrating time-dependent toxicity.

The values of the rate constants were calculated by performing a non-linear regression analysis using the ECt_{50}/LCt_{50} values for various exposure durations obtained from FM 3-11.9.[10] GraphPad Prism® 5.0, which uses the Marquardt-Levenberg method of non-linear regression, was used. The nonlinear regression analysis allowed the values of the model's rate constants to be varied until a set of values was obtained that provided the best fit to the toxicity data. Since the ECt_{50}/LCt_{50} values are derived from constant concentration experiments, the analytical solution to the system of differential equations for the quantity of agent in compartment #1 under the constraint of a constant agent concentration was used in the regression analysis. In order to obtain this analytical solution and use it in the nonlinear regression analysis, several assumptions were made in reference to the toxicity data given in FM 3-11.9 and the underlying experiments used to derive this data.[11] First, the initial conditions for the differential equations were defined by assuming that the initial quantity of the agent in all compartments was zero prior to exposure. As a natural consequence, the initial rate of change for the quantity of agent in compartment #1 was set equal to the rate of uptake from the environment, $b \times C(t = 0)$. Finally, we assumed that the maximum quantity of agent in compartment #1 is the determinant of the toxicological effect. For a constant concentration exposure, this maximum is reached just prior to termination of the exposure, but the maximum may be reached at any time during an exposure to a time-varying concentration.

The analytical solution to the system of differential equations for the quantity of agent in compartment #1 *for the case of exposure to constant concentration* is shown in Equation 9 and the assumed initial conditions are given in Equation 10.

$$Q_1 = bC\left(-\frac{(k_3+\lambda_2)e^{\lambda_1 t}}{(\lambda_2-\lambda_1)(k_3)} + \frac{(k_3+\lambda_1)e^{\lambda_2 t}}{(\lambda_2-\lambda_1)(k_3)} + \frac{1}{k_3} \right) \tag{9}$$

$$Q_1(t=0) = 0 \; ; \; Q_2(t=0) = 0 \; ; \; \frac{dQ_1(t=0)}{dt} = bC \tag{10}$$

[10] FM 3-11.9. op cit., Appendix H.
[11] Ibid.

The constants λ_1 and λ_2 are defined in terms of the model's first-order rate constants in Equation 11 and Equation 12.

$$\lambda_1 = \frac{-(k_1 + k_2 + k_3) + \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_3}}{2} \quad (11)$$

$$\lambda_2 = \frac{-(k_1 + k_2 + k_3) - \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_3}}{2} \quad (12)$$

These equations were used to fit the model to the inhalation toxicity values in FM 3-11.9. An example of how well the model fits the toxicity values in FM 3-11.9, using the parameters derived using this method, is shown in Figure 2, where EC_{50} is the exposure duration-dependent concentration that will cause the specified effects in 50% of the population exposed to the concentration for the stated exposure duration.

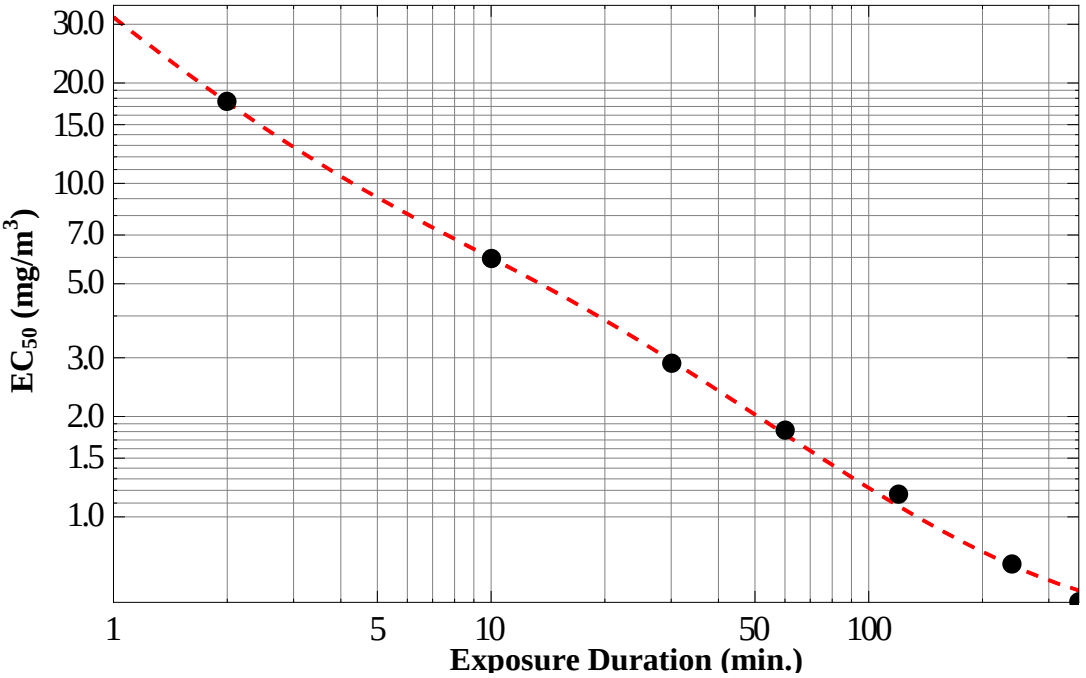

Figure 2. EC_{50} Versus Exposure Duration for Lethal GB Toxicity from FM 3-11.9 (Black Dots) alongside the Curve Predicted by the Two-Compartment Toxicokinetic Model (Dashed Red Line)

Certain assumptions were made about the nature of the rate constants in order to restrict the rate constants to plausible values during the non-linear regression analysis. All rate constants were restricted to positive values because negative rate constants imply reversal of the particular process. In addition, the ECt_{50}/LCt_{50} data for different agents

were grouped based on the toxic load exponent given to each agent in FM 3-11.9 and the individual rate constants were constrained to have the same value across this grouped data set. This constraint ensured that, cumulatively, the values of the rate constants reflected the relationship between concentration, time, and the toxicological effect resulting from a particular value of the toxic load exponent without being specific to a particular agent. In this way the toxic load relationship itself is emulated rather than emulating the trend in EC_{50}/LC_{50} values for a single agent. Table 1 shows how the agents were grouped on the basis of their assigned toxic load exponent in FM 3-11.9. Table 2 gives calculated rate constants for each of the agent groupings assigned the same toxic load exponent. It was found that a single set of rate constants could very accurately describe the EC_{50}/LC_{50} trend with respect to exposure duration for all agents given the same toxic load exponent. Each set of rate constants yielded a goodness of fit (R^2) of 1.000 across all data associated with a particular toxic load exponent. The toxic load exponent can only describe the cumulative effect of the interaction of many different processes and provides no information about the rates of individual processes. The similarities in the assigned toxic load values for different agents do not suggest that the individual processes that govern toxicity are similar in different agents. This does not pose a problem given that the internal processes in this model are not intended to reflect real physiological processes.

Table 1. Agent Groupings Based on the Inhalation Toxic Load Exponent, n_e, in FM 3-11.9[12]

	Agent	Toxicological Effect Level
n_e = 1.5		
	GA	Lethal, Severe, Mild
	GB	Lethal, Severe, Mild
	HD	Lethal
n_e = 1.4		
	GD	Mild
	GF	Mild
	SA	Lethal
n_e = 1.25		
	GD	Lethal, Severe
	GF	Lethal, Severe

[12] Ibid.

Table 2. Calculated Rate Constants for Each Toxic Load Exponent, n_e, under Consideration

Rate Constants (1/min.)	n_e = 1.5	n_e = 1.4	n_e = 1.25
k_1	0.2311	0.1721	0.1599
k_2	0.09145	0.09029	0.1338
k_3	0.01798	0.01138	0.006163

3. Model Limitations and Caveats

Attacks with multiple munitions or environmental conditions involving variable winds may result in intermittent exposures. In these instances, exposure to significant concentrations subsequent to attaining the maximum quantity in compartment #1 are predicted to not result in further injury as long as they do not increase the concentration in compartment #1 beyond the prior maximum. This prediction is almost certainly incorrect. Ideally, the toxicological effect should be correlated to the instantaneous quantity (or concentration) of agent at its site(s) of action within the body, but this approach is not possible without realistic, experimentally-determined, physiologically-based rate constants.

Though this model has been developed with the intention of capturing a mechanistic basis for toxicity, it does not make the distinction between local and systemic effects. The mild effects associated with nerve agent exposure are the result of acetylcholinesterase inhibition at localized portions of the body such as the eyes and skin. Meanwhile, severe and lethal effects of nerve agent exposure are due to acetylcholinesterase inhibition within the central nervous system.

II. MODEL COMPARISON

A. ILLUSTRATIVE SCENARIO

Each of the models described were applied to a hypothetical, realistic attack scenario to demonstrate differences between the models with respect to casualty estimation. The illustrative scenario involved an attack on a light infantry battalion task force in defense of an airfield, involving 816 personnel distributed among 155 stationary locations, shown as triangles in Figure 3. The attack itself was a ground burst from a single long-range tactical ballistic missile with a payload of 250 kg of GB. In this scenario, 129 personnel in 52 personnel locations, shown in blue in Figure 3, were exposed to non-zero dosages of GB and the exposure durations ranged between 3 and 80 minutes.

Agent dispersion was modeled using IDA's GRIDGEN program, which is a modification of VLSTRACK v. 1.6.3 to give BioStrike 2 compatible output. The values of some of the parameters used in GRIDGEN are given in Appendix B. GRIDGEN output is in the form of the dosages experienced at discrete locations on a grid that do not necessarily correspond to the actual personnel locations. IDA's BioStrike 2 program overlays the dosage grid produced by GRIDGEN onto the personnel locations and interpolates between the grid points to find the dosage experienced at individual personnel locations. BioStrike 2 was used in this manner to calculate the cumulative dosages in 1-minute increments at each personnel location. The cumulative dosages were converted to periodic dosages through subtraction. Finally, the periodic dosages in 1-minute intervals were converted to periodic concentrations by dividing the periodic dosage by the 1-minute time interval. In order to generate a continuous concentration profile for each exposed personnel location, a first order linear interpolation of the periodic concentration time points was performed.

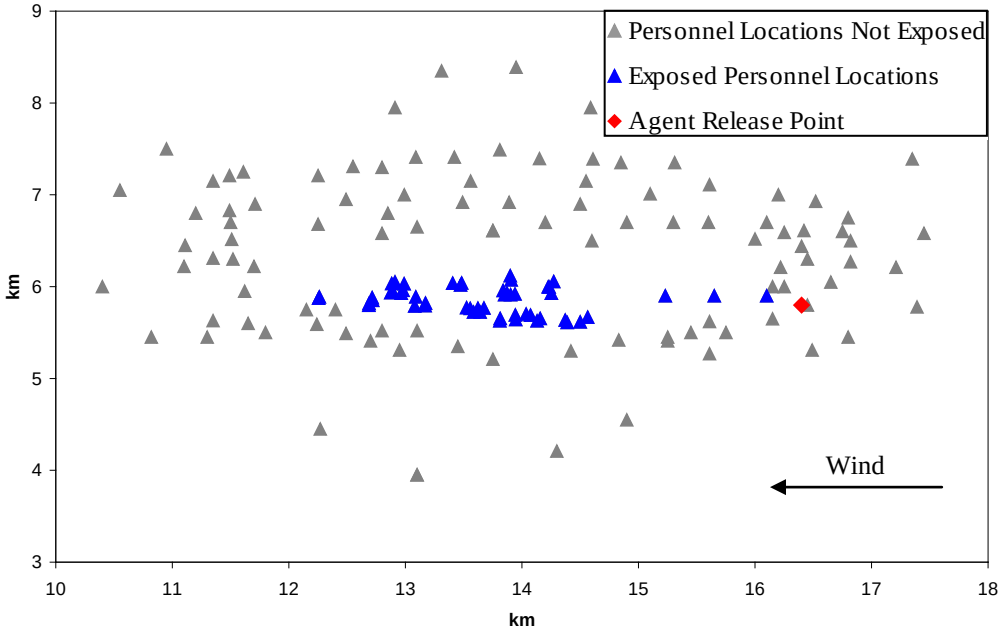

Figure 3. Personnel Locations for the Light Infantry Battalion Task Force in Defense of an Airfield

B. COMPARISON APPROACH

Each previously described toxicity model was applied to this same illustrative scenario, and the number of casualties resulting from the attack was calculated by classifying personnel locations in casualty and injury categories based on the outputs of the toxicity models. The casualty categories were defined by ranges of GB dosages for which an individual was expected to experience no effects/miosis (casualty category #1), become a casualty requiring medical attention (casualty category #2), or become a fatality (casualty category #3) given no intervening medical prophylaxis or treatment. The dosage ranges for each casualty category are given in Table 3. The injury categories were also defined by ranges of dosages, but each of the eight injury categories corresponds to a specific set of physiological effects. The dosage ranges and the physiological effects corresponding to each injury category are given in Table 4. Dosage ranges for both the casualty and injury categories are based on exposure durations of 2 minutes.

Table 3. Dosage Ranges for Casualty Categories Based on 2-Minute Exposure Durations

Casualty Category Number	Cumulative Dosage Low Limit (mg-min./m^3)	Cumulative Dosage High Limit (mg-min./m^3)	Category Description
1	0.00	3.09	No effect/miosis
2	3.09	28.54	Casualty
3	28.54	>28.54	Fatality

Table 4. Dosage Ranges for Injury Categories Based on 2-Minute Exposure Durations

Injury Category Number	Cumulative Dosage Low Limit (mg-min./m^3)	Cumulative Dosage High Limit (mg-min./m^3)	Category Description
1	0	0.4	No effect
2	0.4	3	Dimmed vision
3	3	6	Blurred vision, tight chest
4	6	13	Nausea/vomiting, headache
5	13	22	Bronchospasm
6	22	29	Convulsions, some deaths
7	29	37	Respiratory failure, half die
8	37	>37	Unconsciousness, high mortality

The concept of classifying personnel into casualty and injury categories was adapted from the performance-based human response methodology used in NATO Allied Medical Publication 8(B).[13] The dosage ranges used were adjusted to reflect the toxicity data given in FM3-11.9.[14] This method of classifying by casualty category and injury status was used because the categories bear significance for military medical planning. The classification of personnel into casualty categories gives the medical planner estimates of the total number of personnel entering the medical system, which is useful for determining the patient load and the required medical staff at individual treatment facilities. Classification of personnel by injury category gives the medical planner more detailed information regarding the severity and type of injuries expected, which is useful for allocating specific resources that may be needed to treat particular types of injuries.

This method of categorizing personnel does not reflect the truly probabilistic nature of toxicity. In reality, there is a significant amount of overlap in the dosage ranges

[13] Gene McClellan et al, Consequence Analytic Tools for NBC Operations, Volume 3: Chemical Agent Exposure and Casualty Estimation, Defense Special Weapons Agency Report DSWA-TR-97-61-V3, Pacific-Sierra Research Corporation, Santa Monica, California, September 1998.

[14] Ibid.; FM 3-11.9. op cit. Appendix H.

that are expected to produce mild, severe, and lethal effects. For example, at a dosage necessary to cause 50% of the exposed population to experience severe effects, a significant proportion of the population will die. The distinct dosage ranges for casualty and injury categories assume that there is no overlap in the severity of effects. The use of casualty and injury categories in this analysis is only intended to provide a simplified means to gauge the differences between toxicity models and is not necessarily advocated for implementation in casualty estimation methodologies.

When Haber's Law is used to classify personnel, the dosage ranges given in Table 3 and Table 4 may be used directly without modification. When the integrated toxic load model, the mean concentration toxic load model, or the two-compartment toxicokinetic model is used, the dosage ranges in Table 3 and Table 4 must be translated into values that are meaningful to the particular model. For both the integrated toxic load model and the mean concentration toxic load model, the bounds of the dosage ranges are translated to toxic load bounds by first calculating the constant concentration corresponding to each dosage bound. This is performed by dividing the dosage bound by the duration of exposure, which in this case is 2 minutes. Then, the toxic load expression, Equation 3, is used to calculate a corresponding toxic load value given the previously calculated constant concentration and an exposure duration of 2 minutes. This process is expressed mathematically in Equation 13. The toxic load exponent, n_e, of 1.5 given in FM-3-11.9 was used for GB in this analysis.[15]

$$Bound_{TL} = \left(\frac{Bound_{dosage}}{Duration} \right)^{n_e} \times Duration \qquad (13)$$

The toxic load ranges for each casualty category are given in Table 5 and the toxic load ranges for each injury category are given in Table 6.

Table 5. Toxic Load Ranges for Each Casualty Category

Casualty Category Number	Toxic Load Lower Bound (mg-min./m^3)	Toxic Load Upper Bound (mg-min./m^3)	Category Description
1	0.00	3.84	No effect/miosis
2	3.84	107.81	Casualty
3	107.81	>107.81	Fatality

[15] FM 3-11.9. op cit. Appendix H.

Table 6. Toxic Load Ranges for Each Injury Category

Injury Category Number	Toxic Load Lower Bound (mg-min./m^3)	Toxic Load Upper Bound (mg-min./m^3)	Category Description
1	0.00	0.18	No effect
2	0.18	3.67	Dimmed vision
3	3.67	10.39	Blurred vision, tight chest
4	10.39	33.14	Nausea/vomiting, headache
5	33.14	72.97	Bronchospasm
6	72.97	110.43	Convulsions, some deaths
7	110.43	159.14	Respiratory failure, half die
8	159.14	>159.14	Unconsciousness, high mortality

A similar process is used when applying the two-compartment toxicokinetic model. Again, the constant concentration necessary to produce each dosage bound in Table 3 and Table 4 is calculated given a 2-minute exposure duration. This constant concentration is used to calculate the corresponding maximum quantity of agent in compartment #1 using the analytical solution to the system of differential equations under the condition of a constant agent concentration given in Equation 8. The agent distribution and elimination rates used are those for a toxic load exponent of 1.5 given in Table 2. An uptake rate constant, *b*, of 15 liters per minute was used because the toxicity values given in FM 3-11.9 correspond to this ventilation rate.[16] The casualty and injury category bounds in terms of the maximum quantity of agent in compartment #1 are given in Table 7 and Table 8.

Table 7. Ranges of Maximum Quantities of Agent in Compartment #1 for Each Casualty Category

Casualty Category Number	Max. Quantity in Compartment #1 Lower Bound (mg)	Max. Quantity in Compartment #1 Upper Bound (mg)	Category Description
1	0	0.03700	No effect/miosis
2	0.03700	0.3417	Casualty
3	0.3417	>0.3417	Fatality

[16] FM 3-11.9 op cit. Appendix H.

Table 8. Ranges of Maximum Quantities of Agent in Compartment #1 for Each Injury Category

Injury Category Number	Max. Quantity in Compartment #1 Lower Bound (mg)	Max. Quantity in Compartment #1 Upper Bound (mg)	Category Description
1	0	0.004789	No effect
2	0.004789	0.03592	Dimmed vision
3	0.03592	0.07184	Blurred vision, tight chest
4	0.07184	0.1556	Nausea/vomiting, headache
5	0.1556	0.2634	Bronchospasm
6	0.2634	0.3472	Convulsions, some deaths
7	0.3472	0.4430	Respiratory failure, half die
8	0.4430	>0.4430	Unconsciousness, high mortality

C. COMPARISON OF CASUALTY ESTIMATES

The distribution of exposed personnel among the casualty categories for each of the toxicity models is given in Figure 4. All models predict the same number of fatalities, but differences do exist in the total number of personnel expected to be casualties. The integrated toxic load model, mean concentration toxic load model, and the two-compartment toxicokinetic model predict fewer casualties than Haber's Law. The greatest difference in number of casualties occurs between Haber's Law and the mean concentration toxic load model. For each model, the percent difference in the number of personnel classified into each casualty category relative to the values obtained when using Haber's Law is given in Table 9. The mean concentration toxic load model predicts 26 fewer casualties, which is 32% less than predicted by Haber's Law. Both the integrated toxic load model and the two-compartment toxicokinetic model predict 15 fewer casualties than Haber's Law. This is 19% fewer casualties than predicted by Haber's Law. Approximately 88% of the total exposed population was classified into the same casualty category by all of the models examined.

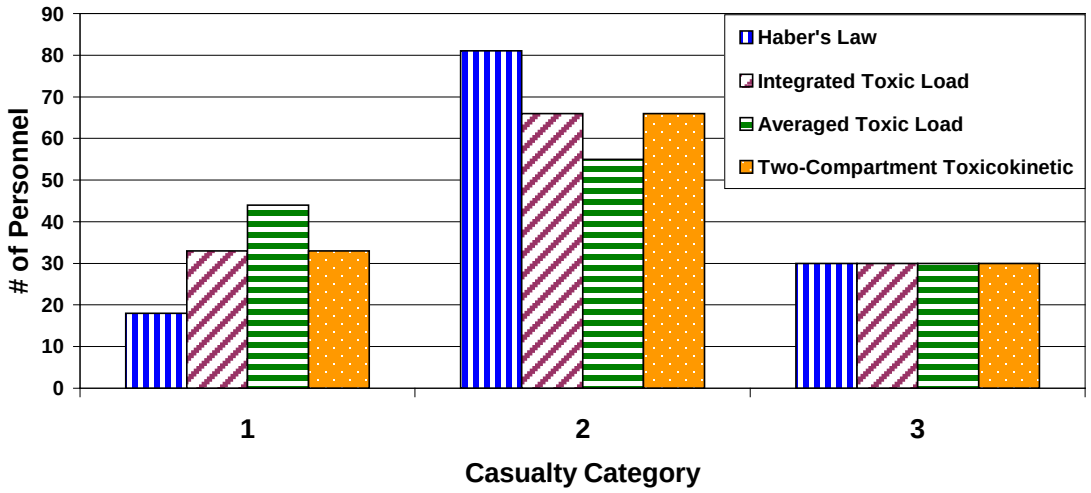

Figure 4. Distribution of Exposed Personnel among Casualty Categories

Table 9. Percent Difference in Personnel in Each Casualty Category Relative to Haber's Law

	Casualty Category		
	1	2	3
Integrated Toxic Load	83%	-19%	0%
Mean Concentration Toxic Load	144%	-32%	0%
Two-Compartment Toxicokinetic	83%	-19%	0%

Because the different personnel locations were occupied by different numbers of personnel and all personnel at a particular location were classified into the same casualty category, it is useful to view the same data presented in Figure 4 in terms of the distribution of exposed personnel *locations* among the casualty categories. This allows the results to not be biased by the number of personnel at each location. The distribution of personnel *locations* among casualty categories is presented in Figure 5. The trends are nearly identical for both personnel and personnel *location*. Over 84% of the exposed locations were classified into the same casualty category by all of models.

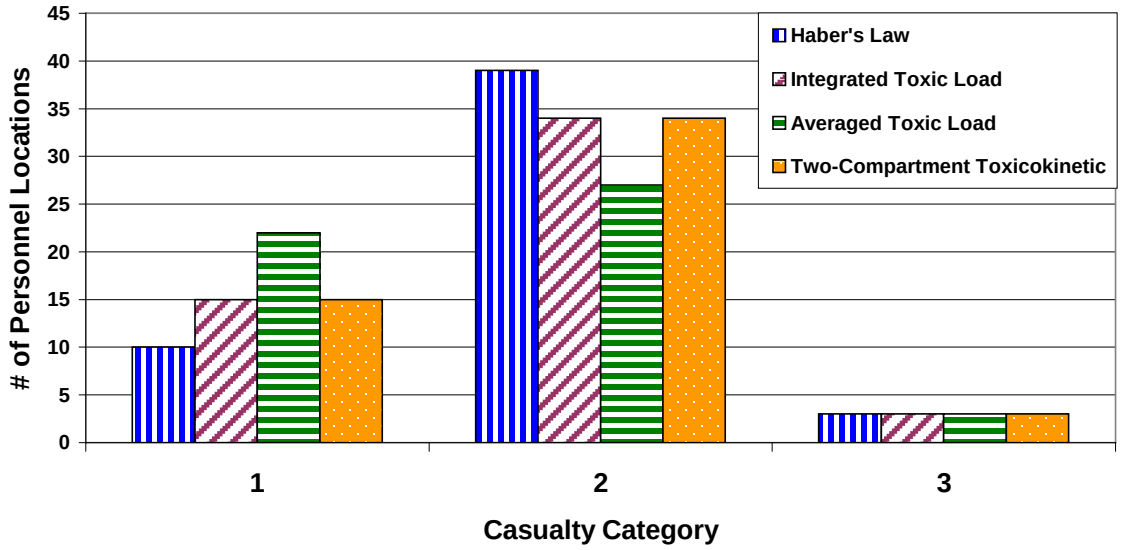

Figure 5. Distribution of Exposed Personnel Locations among Casualty Categories

For a random sample of ten exposed personnel locations, the casualty categories calculated by each model are compared in Figure 6.

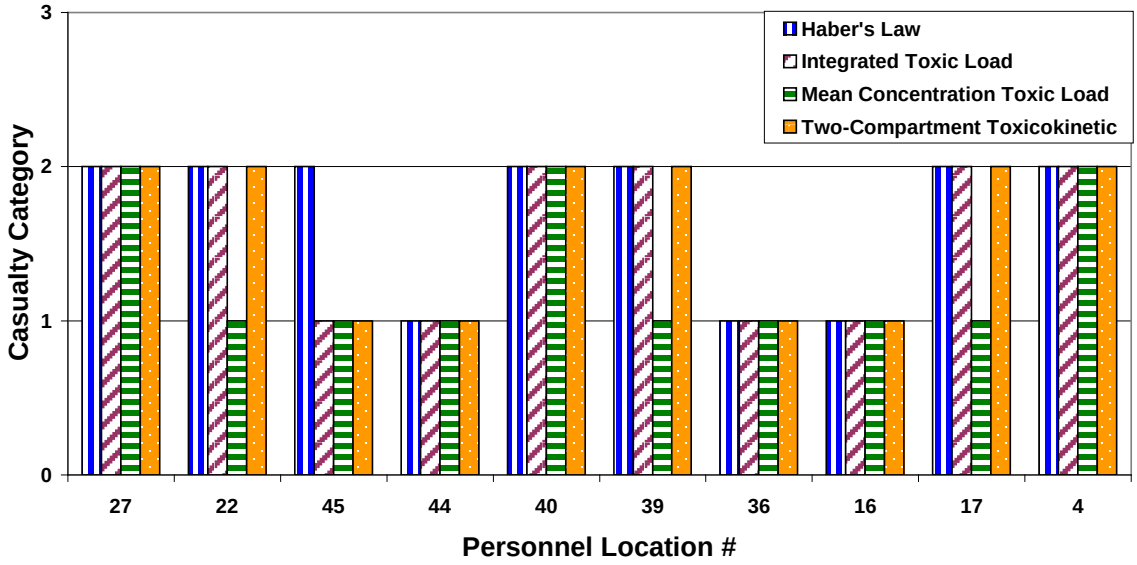

Figure 6. Casualty Category Classification for Ten Sample Exposed Personnel Locations

The distribution of exposed personnel into injury categories is given in Figure 7 and the distribution of personnel *locations* into injury categories is given in Figure 8. Due to the narrow dosage range defining each injury category, the differences between the models appear more pronounced than with casualty classification. For instance, only

53% of exposed personnel were classified into the same injury category by all of the models.

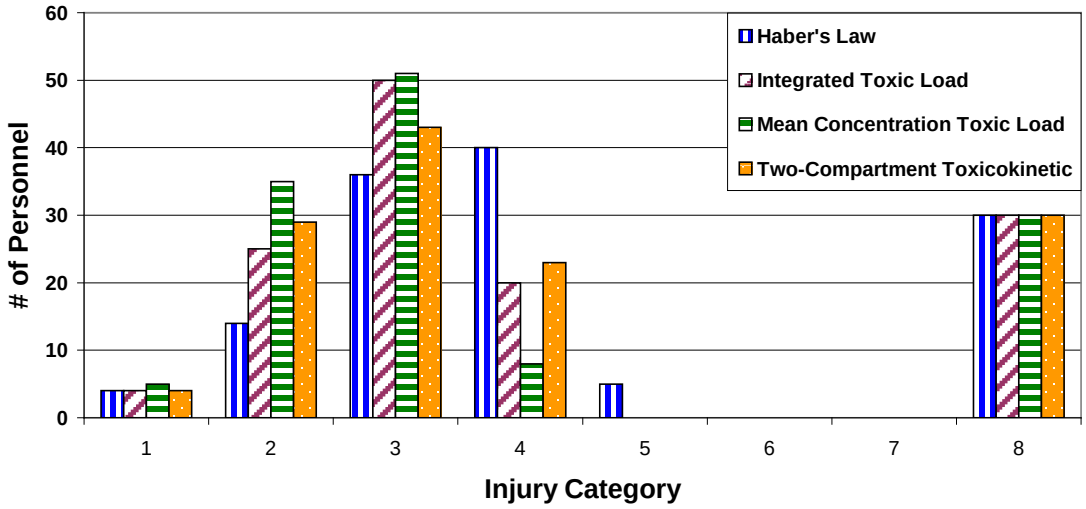

Figure 7. Distribution of Exposed Personnel among Injury Categories

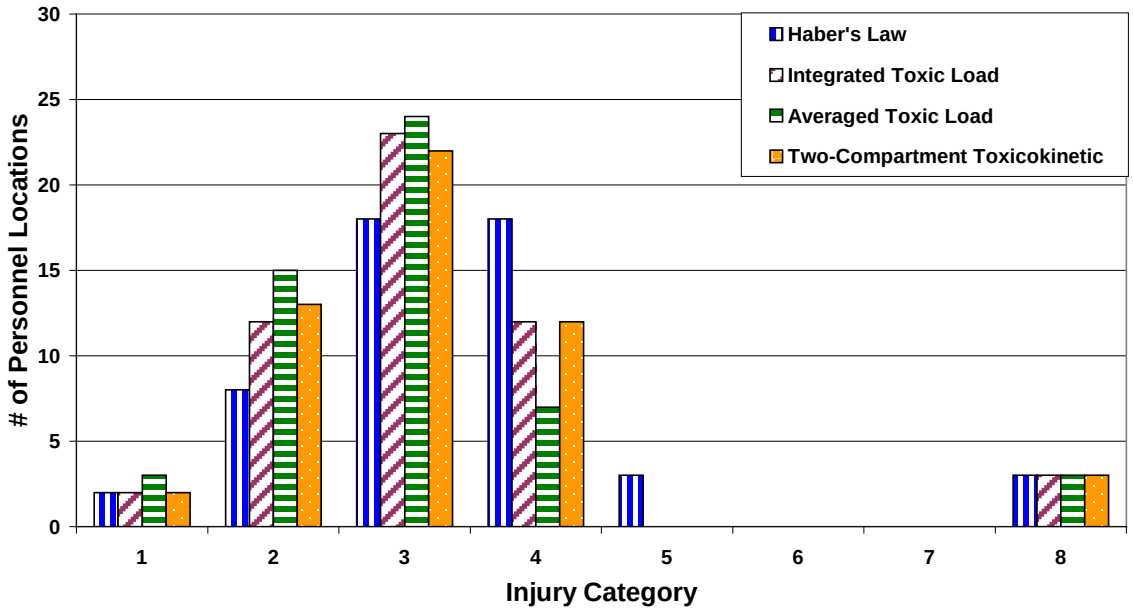

Figure 8. Distribution of Exposed Personnel Locations among Injury Categories

The injury severity classifications of the same set of ten randomly sampled personnel locations for each of the toxicity models are given in Figure 9. Approximately 56% of all exposed personnel locations were classified into the same injury category by all of the models. When differences between the model's expected injury severities do

occur, the differences are rarely greater than a single injury category. The injury category classifications differ by more than a single injury category in only 6% of exposed personnel locations and the differences never spanned more than two injury categories at a single location.

When comparing the casualty category and injury category classification for individual locations, it should be noted that injury categories have dosage ranges that are not aligned with casualty category dosage ranges. As such, it is possible for a location to be classified in the same injury category as another location, yet be classified in a different casualty category. The same effect can be seen when an individual location is classified into the same casualty category by all of these models, but classified into different injury categories.

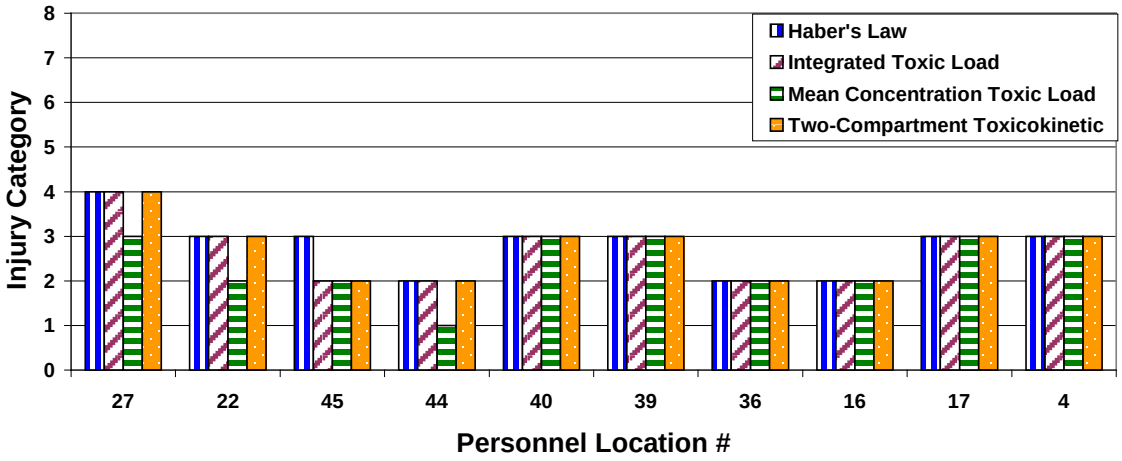

Figure 9. Injury Category Classification for Ten Sample Exposed Personnel Locations

D. DISCUSSION OF COMPARISON

Certain trends in the differences between toxicity model predictions can be recognized through the comparison performed. First, Haber's Law tends to predict more casualties and more severe injuries than the other models.[17] This is likely due to the fact that many of the exposed personnel locations experienced exposure durations greater than 2 minutes. The dosage ranges that define each casualty and injury category are based on 2 minute exposure durations. The other toxicity models predict a decrease in toxicity relative to Haber's Law if exposure durations are longer than those used to determine the dosage ranges used to classify casualties for Haber's Law. Although usually greater than 2 minutes, the exposure durations for the illustrative scenario were relatively short. Other

[17] This result is dependent on the toxic load exponent being greater than 1 for GB. For agents assigned a toxic load exponent less than 1, the opposite trend may be expected.

attacks or meteorological conditions could lead to longer exposure durations and a greater difference in the casualty estimates produced by Haber's Law versus the other models.

Second, the mean concentration toxic load model is generally less conservative than the other models, predicting less severe injury. The process of averaging the concentration resulted in anomalously low mean concentrations when a long period of zero agent concentration occurred between periods of non-zero agent concentrations. This is a direct result of the manner in which exposure duration was defined in this analysis. Because there was no clear way to define exposure duration for these intermittent exposures, this observation was accepted as an inherent property of the model.

Finally, the integrated toxic load model and the two-compartment toxicokinetic model resulted in remarkably similar predictions. Although these two models were engineered to produce identical results under the condition of constant agent concentration, their mechanisms for addressing time-varying agent concentrations are quite different. Because uptake of agent is not instantaneous in the two-compartment toxicokinetic model, large concentration fluctuations that occur on a very short time scale will cause only a minor increase in the quantity of agent in compartment #1. Meanwhile, the integrated toxic load model tends to exaggerate the effects of these fluctuations (for a toxic load exponent greater than one). Scenarios involving these short duration fluctuations may produce fewer predicted casualties with the two-compartment toxicokinetic model than with the integrated toxic load model.

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Appendix A
DEFINITIONS OF TERMS

A. AGENT TERMS

GA – Tabun; Ethyl N,N-dimethylphosphoramidocyanidate
GB – Sarin; Isopropyl methylphosphonofluoridate
GD – Soman; Pinacolyl methylphosphonofluoridate
GF – Cyclosarin; O-Cyclohexyl-methylphosphonofluoridate
SA – Arsine; Arsenic trihydride
HD – Distilled sulfur mustard; Bis-(2-chloroethyl) sulfide

B. TOXICOLOGICAL TERMS

Casualty – an individual that will require medical treatment
Fatality – an individual that will be expected to die given no intervening medical treatment
Dosage – the integral of the agent concentration over the time of exposure
EC_p - the concentration of an agent that produces a given toxicological response in a percentage, p, of the population during a specified exposure duration. For example, exposure to an agent concentration equal to that agent's EC_{50} for the specified duration will produce the particular toxicological response in 50% of the exposed population
LC_p – the concentration of an agent that results in death for a percentage, p, of the population if exposed for the specified duration. For example, exposure to an agent concentration equal to that agent's LC_{50} for the specified duration will result in death in 50% of the exposed population
ECt_p – the dosage of an agent that produces a given toxicological response in a percentage, p, of the population. For example, exposure to a dosage equal to the ECt_{50} for a particular toxicological response will produce that toxicological response in 50% of the exposed population
LCt_p – the dosage of an agent that results in death for a percentage, p, of the population. For example, exposure to a dosage equal to the LCt_{50} for a particular agent will result in death in 50% of the exposed population
Toxicological effect – the injuries, signs, or symptoms resulting from exposure to a toxic substance

C. UNITS OF MEASUREMENT

mg-min./m^3 –milligram-minutes per cubic meter; a unit of dosage that is the result of a product of concentration (milligrams per cubic meter) and time (minutes)
min. – minutes

mg – milligrams

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Appendix B
SELECTED GRIDGEN PARAMETER VALUES

A. METEOROLOGICAL PARAMETERS

Time: 1900 hrs.
Wind speed: Constant, 8 km/hr.
Temperatures: 25 degrees Celsius for minutes 0 to 60, 17 degrees Celsius thereafter.
Cloud Cover: Clear
Pasquill Stability Category: Neutral

B. MUNITION PARAMETERS

Fill weight: 250 kg
Height of release: 0 m Ground burst

C. AGENT PARAMETERS

Agent: GB
Droplet mass median diameter: 500 microns
Droplet size distribution sigma: 1.7 microns
Horizontal and vertical cloud sigma: 6 meters

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14. ABSTRACT

Four toxicity models are compared to asses the significance of using different toxicity models for military medical planning. The four models examined are Haber's law, the integrated toxic load model, the mean concentration toxic load model, and a two-compartment toxicokinetic model. All of these models are applied to the same hypothetical attack scenario and the personnel exposed in the attack are classified into categories according to casualty status and injury severity. For this scenario, Haber's law was found to predict the greatest number of casualties, while the mean concentration toxic load model predicted the fewest, 32% fewer than Haber's Law. The integrated toxic load model and the two-compartment toxicokinetic model predicted the same number of casualties for the scenario investigated. A discussion of the resulting casualty estimates provides insight into the conditions under which the different models may lead to different results.

15. SUBJECT TERMS

Toxicity, Toxicity Model, Toxic Load, Haber's Law, Toxicokinetic, Pharmacokinetic, Chemical Warfare Agents, Integrated Toxic Load, Mean Concentration Toxic Load, GB, Military Medical Planning.

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